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Prospective Open Case Control Comparative Study of Intraarticular Injection of Low and High Molecular Weight Viscosupplement in Osteoarthritis of Knee when given with and without Steroid and to assess the Use of C-arm in Target Delivery of Viscosupplement in Knee Joint Cavity

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Abstract: ***Aim:*** *To study the role of viscosupplement in osteoarthritis of knee joint from KL grade-2, 3 and 4. To compare the efficacy between low with high molecular weight viscosupplements. To assess the frequency of its use when it was given with and without Steroid. To study the role of C-arm in intra-articular viscosupplementation of OA knee.* ***Objective of the Study:*** *Indians become affluent and most of them are obese and fortunately, their life expectancy has been increased, only to welcome the early onset of osteoarthritis, and in particular OA knee. Unfortunately, just because of the hard work, it never even leaves the poor. Sadly, whether they are rich or poor, they vehemently oppose or reluctant to accept for the surgical replacement of joints. Thus, to study the effect of intra-articualr injection of low molecular and high molecualr weight (20,000 and 60,000 daltons) viscosupplement in OA knee with and without steroid and look for the frequency of requirement for repeat dose of HA and to assess the use of C-arm in delivering viscosupplement into joint cavity as against routine practice of giving HA through sub-patellar route.* ***Material and Methods:*** *We have enrolled 358 patients (104 males and 254 females) of osteoarthritis of knee with radiological Kellgren and Lawrence (K&L) grades 2 to 4 based on X-rays of knee taken in AP in standing view. Pain was evaluated by VAS, and performance was assessed by 50 foot walk time. We categorized the patients into KL grade 2 (M 24 & F 82); KL grade 3 (M 41 & F 112) and KL grade 4 (M 39 & F 60). We have randomly picked up and formed into group-A & B. 178 cases are kept in group-A with KL grade-2 (M22 & F37), KL grade-3 (M27 & F52) and KL grade-4 (M21 & F19). In group- B, we have selected 180 cases from KL grade-2 (M24 & F44), KL grade-3 (M29 & F40) and KL grade-4 (M 19 & F 24). In group- A (n-178), 85 cases allotted for low (M32 & F53) and 93 cases for high (M40 & F53) molecular weight viscosupplement without steroid and it was kept as control for Group-B. In group-B (n-180), 86 cases have been selected for low (M32 & F54& and 94 cases for high (M40 & F54) molecular weight viscosupplement with steroid. The low molecular weight HA was given as weekly once for five weeks and high molecular weight viscosupplement was given as single dose. From group- A and B, we randomly selected 211 (60.75%) cases (37 & 52 from group- A and 40 & 82 from group- B) for assessing the role of C- arm in delivering viscosupplements into knee joint cavity, because knee joint cavity is well away from sub-patella and in KL grade 3 and 4, joint cavity is narrow or asymmetrically present with valgus and varus deformity and thus, viscosupplement was given under the guidance of C-arm for appropriate target delivery. We asked them stay in bed for 8 to 24 hours for the even distribution and allow the HA to get complete percolation in the fissured cartilages and for the remaining cases, viscosupplement was given into knee joint as the routine sub-patellar route on lateral approach.* ***Results:*** *Mean age of patients 52.4 years (range 39-74 years); with male: female ratio of 1:2.44. Early feel good response in group-A and group-B were assessed by VAS from 0 to 100. Before and after the viscosupplementation, visual analogue scale was compared with both group. In group-A, before viscosupplement, 100% pain was noted in 82 patients, and 50% pain was seen in 61 cases, whereas after viscosupplementation, more than 50% pain relief was noted in 92 cases (31 in LMW HA and 61 cases in HMW HA). In group-B, as per VAS, 100% pain in 85 patients and 50% pain in 70 patients are have been noted, whereas after HA, more than 50% pain relief and early feel good response was noted in 152 patients (68 in LMW HA and 84 patients in HMW HA). Pre and Post procedures, the performance was assessed by 50 foot walk time. In group-A, in low molecular weight HA category, before viscosupplement, they take 76 seconds to finish 50 foot walk and whereas after the procedure, they able to complete 50 foot walk in 68 seconds, and in HMW HA category, before visco, they need 68 seconds, and after the visco, only 42 seconds are required to complete the target. In group-B, in low molecular weight category, before the procedure, patients took 72 seconds for 50 foot walk and whereas after the procedure, only they needed 36 seconds and in HMW HA category, before visco, it was 81 seconds and after visco, they quickly complete 50 foot walking distance in 26 seconds. (Fig.13,14)In this study, we have looked in to the role and benefits of C-arm for the administration of viscosupplement, and it reveals that, C-arm guided hyaluronic acid directly in to the joint cavity cases are performing well and they have long lasting effect, as 31% in LMW HA and 64% in HMW HA in group-A, and in group-B, 73% and 98% in low and high molecular weight viscosupplement, respectively. In those who have received viscosupplement through conventional sub-patellar route, their results are not satisfactory than C-arm guided, and it was found in group-A with low MWHA at 14%, and in high MWHA at 36% and whereas in group-B, 48% in low MWHA with and 59% are in high molecular weight HA. After 3rd, 6th, and 9th month follow up, 34% in group-A and 86% in group-B with high MWHA patients had high level performance in pain free walk and gait and whereas at 24th month follow up, still 59% of the group-B patients with high molecular weight HA with steroid, continue to have high level performance without NSAIDs whereas in group-A with low MWHA without steroid had no benefits was noted at 3rd month review and in group-B with low molecular weight HA with steroid has persistence of pain free walk, 38% at 3rd month, and 17% at 6th month and beyond that, no appreciable responses was seen by them. From our study, it clearly reveals that high molecular weight HA in both group A (without steroid) and group-B (with steroid) are having excellent clinical benefits in osteoarthritis of knee and its statistical analysis with student-t test in both group-A and B category are having the p- value of 0.0001 whereas low MWHA in both group-A and B are not statistically significant. Likewise, early feel good responses, reduction in pain and swelling are good in high molecular weight category*

(61 cases in group-A & 84 cases in group-B). 50 foot walking time, in group-A, improvement was noted from 76 to 68 seconds with LMW HA and from 68 to 42 seconds with HMW HA, and whereas, in group-B, remarkable benefits was seen, that is 72 seconds to 36 seconds in LMW HA and 81 seconds to 26 seconds in HMW HA and statistically extrapolating the 50 foot walk time in both group-A & B, has shown the P-value of 0.001 and it infer that, this value is statistically significant for high molecular weight viscosupplements. Next repeat dose for high molecular weight HA in both group- A & B and with those with KL grades-2 & 3 are not required even at 24th month of visit but 28% of KL grade-4 cases, required repeat dose after about 6 to 12 months. The missing for next doses are high in both group-A and B category of low MWHA with 34% (28.9 cases) and 21% (18.06 cases), respectively. Conclusion: Viscosupplement was found to be quite useful modality of treatment in osteoarthritis of knee with KL grade 2 & 3. Early feel good responses and reduction pain on visual analogue scale was seen in high molecular weight category of group-A & B cases than low MWHA categories. On 50 foot walking time; Group-A cases who received high molecular weight viscosupplement can able to complete in 42 seconds as against 68 seconds before the procedures, whereas Group-B cases with high molecular category can finish off the 50 foot walk distances in 26 seconds as against 81 seconds before the procedures. Steroid with viscosupplement have quickly relieved their pain and improved the mobility. C-arm is surely useful in target delivery of viscosupplement into the joint cavity, and they perform well in early feel good responses and this effect is last long than when it is administered by blind sub-patellar route. In KL grade-4 OA knee, when they are unfit or not willing for surgery or presence of comorbid conditions, viscosupplement can give 40% functional improvement in pain and gait and 28% might require repeat dose of viscosupplement in 6 months to 12 months. Ask them to give "pain killer holiday" whenever, no pain, less or tolerable pain, it is better to bear the pain and put full stop to pain pills. Future of osteoarthritis patients are looks bright, when they report early to appropriate clinician, they can give "not pain free but disease free life".

1. Introduction

Worldwide statistics on osteoarthritis reveals that, over 100 million people suffer from OA, and it is one of the most common causes of disability (Hinman RS et al 2010; Heiden T et al 2009). In India, the prevalence of osteoarthritis is reported to be in the range of 17-60.6% (Sharma MK et al 2007). Epidemiological profile of this disease in India is not clear but it is estimated that osteoarthritis (OA) is the second most common rheumatological problem and the most frequent joint disease with prevalence of 22% to 39% in India (Chopra A et al 2001). Currently, in America, OA is the second most common form of arthritis, whereas ischemic heart disease, still unbeatable in the first place. OA is the common disability after 50 years of age for admission than rheumatoid arthritis and probably this number will swell with the addition of aging plump and bellies population. The demand for primary hip and knee arthroplasty in the United States is expected to increase by 174% and 673%, respectively, by 2030 (Colin D Mathers et al 2002).

Pain control is often inadequate when OA progresses to a severe disabling stage. Thus, early detection and intervention are the essential aspect for the improved care of this disease or else, in future, across the globe the job of the caregiver for these ailments are going to be more demanding.

As per Indian planning Commission 201, osteoarthritis accounts for half of all chronic conditions in persons aged over 65. India is expected to be the chronic disease capital, thus, Piramal Healthcare Limited has conducted nationwide campaign against chronic diseases, and they have observed that over 60 million people could suffer with disabling arthritis or degenerative joint diseases by 2025. The true prevalence of OA, however, varies greatly depending on the kind of definition used, age, sex and geographical area studied. When radiographic definition applied, the prevalence of OA can be very high. Prevalence increases with age, so that about 11% of all women over the age of 60 years have symptoms due to knee OA. Knee osteoarthritis is the most common condition which represents a major contribution to the burden of physical disability (Felson DT et al, 1987). The heterogeneous etiology of OA contributes to the challenge in treating it and finding effective disease-modifying drugs.

OA is the failure of repair of damage that has been caused by excessive mechanical stress on the joint tissues. Without attempting to contain or correct the mechanical insult, any attempt at healing is bound to fail. When the joint in the same adverse environment, it is unlikely that any drug can inhibit the pathogenic cytokine pathways of cartilage breakdown and added to that, it adversely increases the synthesis of cartilage matrix molecules by the chondrocytes. In the background, the subchondral bone is playing a critical role in containing the mechanical abnormalities that damage the cartilage, mere emphasis on cartilage repair is useless, unless the operating abnormal stresses are reduced. If, that is done effectively, the so called disease modifying OA drugs (DMOAD) are likely to be unnecessary.

To make readers to understand better, like any one internal organs goes for failures, similarly synovial joints too can fail, and at the beginning, osteoarthritis can be quite asymptomatic, as everyone aware of asymptomatic phases are there for every other organs such as heart, liver and kidney failures, at initial stages but only to precipitate with profound symptoms after sometime. The affected joint tissues can release proteoglycans and it quickly increases the expression of genes for stromelysin, aggrecanase and tissue inhibitor of matrix metalloproteinase (TIMP) by chondrocytes, leading to degradation of joint tissues.

1.1 What is osteoarthritis?

Osteoarthritis is a chronic, progressive disorder of synovial joints with gradual loss of articular cartilages, due to different etiologies and it eventually destabilize the entire structures of the joint as an organ and ultimately result in similar clinicopathological and morphological outcome. The structural changes that take places are uneven and irregular loss of cartilage over habitually load or weight bearing areas of joint with fissuring, fibrillation, ulceration, reduction in proteoglycan, loss of thickness of cartilage and joint space, with an alteration in the peculiar features of cartilaginous compressive, tensile, shear forces, and its liquid permeability, which causes increase in water and cell swelling with resultant worsened intra-articular pressure, thereby it, exposes the underlying bone, leads to formation of eburnation, subchondral sclerosis, focal necrosis, subchondral cyst, and marginal osteophytic growth. The

affected joint swelling can be due to condylar enlargement or by inflammation of synovium and effusion. Thus OA is the net result of imbalance between synthesis and degradation of chondrocytes, extracellular matrix and subchondral bone.

Often OA is due to some or other form of congenital, developmental, structural abnormality, and other additional risk factors like obesity, ligamentous instability, imperfect alignment, incoordination and microtrauma of the joints. Therefore, it indicates that osteoarthritis is always due to secondary to one or other form of complications. There are points argue in favour of OA as secondary that, when IA stress is relieved, there will be symptomatic and structural improvements are noted, after wedge osteotomy, orthotics like medial and lateral insole footwear and braces, etc. Obviously, it implies that, also in primary OA, that same IA stress is expected to play as the predominant and precipitating cause. The unique factor which precipitates IA stress is not that imperfect alignment but it is effect of imperfect alignment and the severity of OA is determined by the ability of joint to withstand the stress than just that faulty alignment. Knee joint damage can be seen either in medial, lateral tibiofemoral and in patellofemoral compartment and when it involves all three compartments are called generalized OA knee.

There are some modifiable and non modifiable risks factors are exist for the development or precipitations of OA are present. Among these, obesity is the most significant and greatest modifiable risk factor for an OA, leads to decreased mobility and negative impact on quality of life. Coggon et al reported that BMI > 30kg/m^2 is associated with 6.8 times risk for OA knee and it is directly related to OA, both by excessive joint loading or by altered biomechanical patterns. Rise of 2 units of BMI, leads to 36% chances of OA knee.[1-3] Leptin is a 16- kd protein product of the obese gene (ob) and is produced primarily by adipose tissue. It acts centrally in the hypothalamus to regulate food intake and energy expenditure. Plasma leptin levels will be high in overweight individuals and it falls once they reduce weight. As per the article, leptin affects subchondral bone and it can theoretically play an important role in pathogenesis of OA. This constitutes the rationale behind disease modifying therapy through therapeutic strategies to counteract dysregulation of this proinflammatory adipokine production.[4,5] Weight loss improves both symptoms of OA and it can slow the progression of OA. Study has proved that elimination of overweight could reduce the incidence of OA knee by about 25% to 50% and OA hip by 25%. [6] Certain occupations like farmers, house wife, drillers, ballet dancers, and some sports injuries are can promote or worsen OA.

Likewise, certain non modifiable risk factors for OA, such as age advances, the incidence of OA are increases by systemic and local factors, obesity, ligament laxity and impaired neuromuscular joint protective mechanism in old ages. In more than 80% of people after the age of 60, radiological evidence of OA are present. In the Framingham study, the prevalence was 30% between ages 65 to 74 years. It is thought that, increased incidence of microdamage to articular cartilages is the probable reasons for OA in the elderly population. But the incidence of OA in both sexes appear to be the same at and after 80 years of age.[7]

More than a decade of my experience on 4697 osteoarthritis patients at two different centres from August 2006 to June 2018 (Rheumatology OP in Govt. Mohan Kumaramangalam Medical College Hospital and Akitha Hospital, Centre of Excellence for Autoimmune diseases, Salem, TN State, India) have shown that female outnumber the male in all categories of OA (male 33.33% (n-1565.51) and female 66.67% (n-3131.48) but more are less equal in both sexes after 70 years of age. (Fig.1) Among both sex, OA knees are common, and unilateral OA knee is the usual clinical presentation in age group less than 50 years but after fifty, bilateral knee involvement was noted. Second commonest one is hand OA, and the least one is OA of elbow joint. (Fig.2) Again, obesity associated with OA is also exist in female more than male (12.73% (n-597,92) & 3.85% (n-180.83) (Fig.3) and likewise obesity, osteoarthritis and flat foot association was found in 8.20% of female (n-385.15) and 1.82% of male (n-85.48).

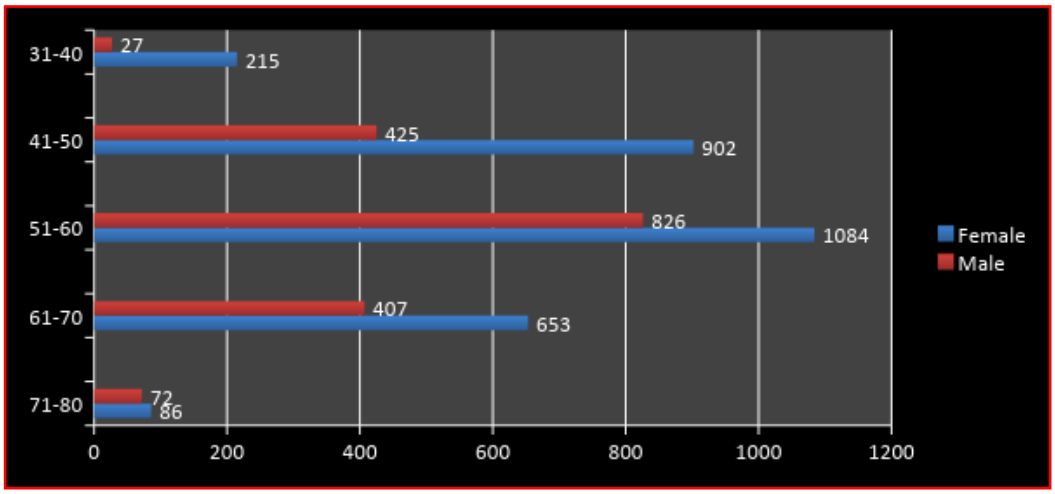


Figure 1: Age and Sex wise Incidence of Osteoarthritis

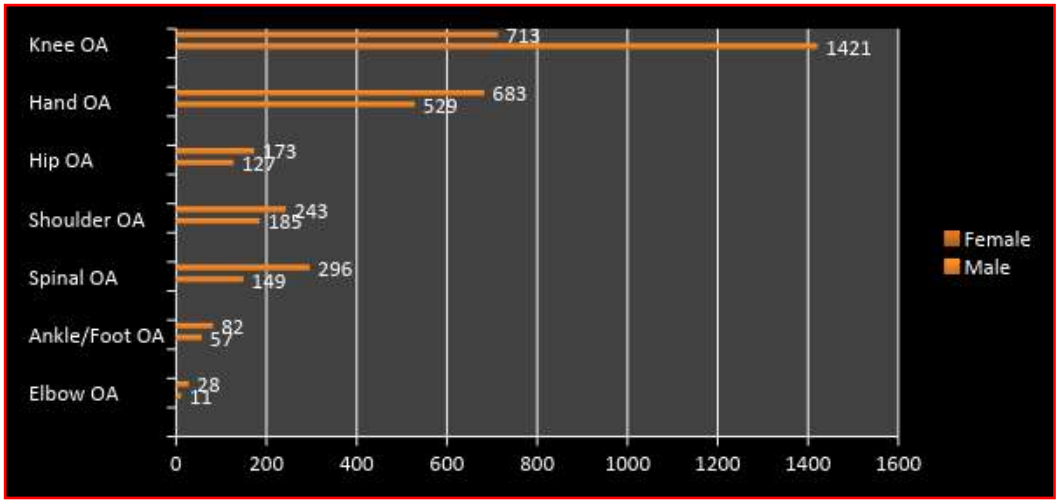


Figure 2: Joint Wise Incidence of Osteoarthritis

A community-based cross sectional study was carried out in an urban resettlement colony in South Delhi to study the prevalence of knee osteoarthritis in women aged 40 years and treatment seeking behavior of women suffering from osteoarthritis, found 47.3% of women (123/260) are suffering from knee osteoarthritis. In general, OA knee is more common in Indians whereas hip OA in European populations with a sharp distinction that OA hip also can be seen in poor Indian farmer, due to the habit of carrying weight on head.

In female the onset, initiation or progression of OA is better explained by the presence of oestrogen receptors in chondrocytes and women who use HRT has less prevalence for OA than the counterpart, and the incidence of OA knee and hand are twice more common female whereas hip OA was seen more in men.[8] When there is a muscle weakness around the knee joint, like quadriceps wasting or atrophy, the brake on the pendular action of lower limb is lost or reduced. When this stabilizing effect of knee is lost, the mechanical stresses on the joint will increase, which result in OA knee.

In addition, OA seems to be greater and rapidly progressive in menopausal age group of women than men and this suggests that post menopausal oestrogen deficiency increases the risk of OA and as per clinical trials, HRT may prevent pathological changes in OA but not the symptoms of OA. The disease progression is three times more and progresses rapidly in people with low vitamin D3.[9-11]

Often there won't be any correlation between the amount of pain and radiological signs of OA. Some have severe degenerative changes, osteophytic overgrowth, subchondral sclerosis and JSN (Joint Space Narrowing), but they are asymptomatic. On the contrary, quite number of patients, report to clinician with severe pain in knee or hip, but nothing abnormal seen radiographically and the severity of symptoms and radiological findings never have correlations.Liang precisely expressed this issue in few words "x-ray don't weep but patient weep".[12] Recent recommendations of the European League Against Rheumatism (EULAR)14 for the diagnosis of OA knee suggests the presence of three symptoms- persistent knee pain, brief morning stiffness and reduced function and three findings on physical exam- crepitus, bony enlargement, and restricted motion- the probability of having radiographic knee OA was 99%, but it was only 19% when persistent pain alone was considered.

1.2 Anatomy and Physio-biochemical Changes in Synovial Joints

In normal joint, healthy water rich articular cartilage forms a soft cap on top of the bones, and it provides a low friction surface that facilitates smooth articulation of opposing bones. Chondrocytes are the only cell type present in cartilage, and they synthesize a large volume of extracellular matrix, which gives the tissue its mechanical properties and hence enable its articulating function. The components of the ECM are the protein collagen and the proteoglycan aggrecan.

Type II collagen, a triple helical protein that forms strong, rope like molecules which are cross linked to form fibrils, provides mechanical strength to articular cartilage. These are arranged tangentially near the articulating surface, and radially deeper within the tissue, to dissipate mechanical forces acting on the tissue.

Aggrecan is a proteoglycan, composed of a protein to which are attached many glycosaminoglycan (GAG) side chains. The protein core is folded into three globular domains (called G1, G2, and G3) separated by interglobular regions. The GAGs proteins like chondroitin sulfate and keratan sulfate are attached in the extended region between G2 and G3. The GAGs are highly negatively charged, which draw water into the matrix and causes hydrostatic swelling of the matrix, providing resistance to compression or shear forces.

The ECM is organized into different structural and functional regions. These can broadly be divided into pericellular matrix (PCM), which surrounds individual chondrocytes, and the further removed matrix. Type II collagen and aggrecan are distributed in the further removed matrix and are largely absent from the PCM. The PCM is enriched for growth and regulatory factors that modulate the behaviour of the chondrocyte. The PCM contains fibroblast growth factor 2 (FGF-2) that is released in response to mechanical loading and acts on chondrocytes through cell

surface FGF receptors. Thus the extracellular matrix has two principal functions: (1) to withstand mechanical load and (2) to sense and respond to changes in the mechanical environment in order to maintain tissue homeostasis.

1.3 Pathology

Chondrocytes are responsible for the production, maintenance, remodeling and eventually destruction of the cartilaginous matrix. Metabolic activities of chondrocytes are low and it can survive even in low hypoxic state. Hypoxic stimulus regulate the intracellular expression of hypoxia inducible factor-1α (HIF- 1 α), which support the survival of chondrocytes. The nutrients for the cellular activities of chondrocytes are obtained from synovial fluid and subchondral bone. Perhaps, chondrocytes per se has limited regenerative capacity and so whenever, significant injuries are there, it often predispose to OA (Dell'accio and Vincent, 2010).[13]

In early stages of disease, chondrocytes appear to adapt to local stress, by proliferation of chondrocytes in clusters, which alter the ECM by expressing markers of inflammation like collagen type X, VEGF and matrix metalloproteinase 13. Chondrocytes go for progressive destruction, cell death by apoptosis and necrosis by release of the matrix degrading enzymes and cytokines. Even before clinical symptoms start, the smooth surface of the articular cartilage becomes roughened with small small's irregularities and superficial clefts. When the disease is unchecked, the cracks become deeper, extend up to middle zone of cartilage. When these lesions grow and connect each other, damaged surface area is increased. Cleft becomes eroded and ulcerate and finally exposing the underlying subchondral bone. Subchondral bone is a global term that includes the subchondral bone plate, underlying trabecular bone and bone marrow space. Subchondral bone remodels itself and appears like an ivory, dense substance with a smooth surface and it is called eburnation. Further, it progresses with formation of new bone at the joint margin (osteophyte). Subchondral cysts are formed either by influx of synovial fluid or by local necrosis of bone and bone marrow oedema.[14-16] Pathogenesis OA knee is beyond the scope this article.

1.4 Clinical Features of Osteoarthritis

OA is the most common musculoskeletal disease causing high rate of physical and functional disability. Occurrence of OA is on the rise due to addition of aging population every year and they are already almost equal to the middle age population. Unfortunately, across the globe, due to increase in the plumps and bellies population, the OA is no longer considered as diseases of old, but truly the problems of the middle ages too. As a result of these, we see lot of OA segment of patients even below 50 years and they often find difficult to accomplish their own jobs of daily needs, work day absenteeism, loss of works and income or women with household chores, which directly or indirectly affect quite large number people and in addition, they are also have disturbed sleep, depression and other psychosocial disorders. Added to this, chronic and persistent pain in OA and sometimes, even in post joint replacement patients are experiencing joint pain due to recently recognized, enhanced central neuronal signaling which are arise remote from the affected joint.

1.5 Osteoarthritis of Knee

Overall prevalence in the elderly population is about 24%, and at least about 8% could be seen in middle age and obese people. In young and middle ages, obese females are more affected than male. By 2050, as per North American literature, about 66 to 100% of people above 70 to 80 years are going to develop OA knee. Indians and Chinese have increased incidence of severe OA knee. Farmers, miners, people carrying excess weight on head and other jobs which require frequent bending of knees are more prone for OA knee. It can involve either one of medial and lateral tibiofemoral compartment and the patellofemoral compartment. The precise location of pain can be helpful for locating the compartmental OA, like, when pain is present in outer aspect of knee in obese female or male with genu valgum, they will be having lateral TF OA. Likewise, when pain is present on medial aspect of knee with genu varus and anterior knee, it is probably due to medial TF and patellofemoral OA respectively. The patellofemoral OA pain usually presents during climbing or descending stairs or while get down from buses and it occasionally leads to buckling of knees and falls. Valgus and varus deformities can directly affect the range of movement and accelerate the cartilage injuries, subchondral sclerosis and joint space narrowing.

2. Symptoms

2.1 Pain and Stiffness (Pain in OA, "worsened by work and relieved by rest")

Pain is the troublesome symptom. In early OA, they often feel pain after brief exertion. Later, they will notice pain while getting up from squatting, climbing stairs, and running and followed by pain even at rest. They feel period of gelling (stiffness) of joint for some time, before becoming relieved from pain, and it last only for about 30 minutes. This is often called as "first movement pain". Pain disturbs the sleep by hitting of condyles by muscular relaxation or by increases in joint effusion at rest. Pain usually presents on both sides of knee, sometime, one side more than other. There will be difficulty in kneeling, and difficulty in sitting and getting up from Indian style sanitary ware. Female with OA, they have difficulty in performing household chores. Frequently, there won't be any correlation between painful limb and radiological signs of OA. Sometime, patient particular stance will aggravate the joint pain, that is, if they stand on one leg, that side of joint will receive 2/3 of body weight; therefore, the pain, damage, disability and deformities are further worsened. Frequent locking of knees and difficulty in extending the flexed knees are present due to loose bodies or fragments of cartilage in the joint space. Sometime, they feel friction or grunting sounds in knees while walking due to meeting of roughened and irregular cartilages. Buckling or "giving way" feel in knees can be appreciated by patients, which can be due to quadriceps wasting, meniscus lesions, ligamentous laxity or slip of patella from intercondylar fossa due to condylar displacement by unicompartmental OA knee. Occasionally,

pain may be present, much lower than knee joint, and over medial side, that is due to anserine bursitis. Posterior knee pain can be due to tense effusion or by ruptured or infected baker's cyst. Their gaits become altered by bowing of legs, knock knees, shortening of limb or disparity in limb height, and by fixed flexion deformity. OA may be associated with depression and disturbed sleep due to pain, cost of treatment and foresee huge expenditure for surgery etc.

Box 1: Cartilages are anerve structure and it is insensitive to pain

Suspected Causes of Pain in OA Knee

Periosteal and subchondral bone
Intraarticular ligaments
Pressure on subchondral bone
Venous engorgements
Intramedullary or joint cavity Hypertension
Capsular distension or stretching
Synovitis
Osteophytic outgrowth
Tendonitis
Fasciitis
Bursitis
Stretching of Nerves by pressure
Central sensitization of pain

2.2 Swelling

Mild to moderate swelling of knees are present, usually one side more than the other. They often have suprapatellar effusion and with baker's cyst, patellar tap can be elicited. About 20 to 30% of patients come to us with severe and tense swelling of one leg, with warmth and tenderness of calf muscle, which is due to ruptured baker's cyst. It often misleads to think as DVT. Why it is important, because, Moses sign and Homan sign are also positive in this condition, thus there will be error in clinical judgment. Just look for crescent sign (semilunar shape swelling around medial and lateral malleolus) with subcutaneous oedema. If present, that is probably due to ruptured baker's cyst.

2.3 Signs

There will be reduced range of movement, and pain on extremes of joint mobilization. Mildly warm and is tender. One can appreciate patellar tap, fluid thrill, joint crepitus (sometimes audible) or locking of knee whilst moving due to presence of loose bodies in joint cavity. Patella may get jetted out from intercondylar fossa. Knee looks enlarged due to condylar enlargement, synovitis and partly due to osteophytic growth.

In secondary OA, condylar enlargement is not usually present, but effusion, deformity and subluxation of joints may appear as enlarged joints. Decreases in anterior and posterior laxity of joint are associated with reduced joint space. 80 - 90% of patients have bow (varus) knee due to medial femorotibial compartment OA, whereas 10 – 20% has knock (valgus) knee, due to lateral tibiofemoral compartment OA.

Periarticular structure examination can aid in identifying anserine bursitis, infrapatellar and prepatellar bursitis. Instability of knee may be present, due to damages to protective mechanism of muscles and ligaments. Always look for quadriceps wasting and when Lachman's test and posterior drawer tests are positive it denotes, injuries had happened to ACL and PCL respectively. Altered gait patterns can be caused by a conscious or subconscious attempt to protect the joint or to minimize the pain.

When knee jerk absent, there should be discovertebral or spondylophyte compression of (L3) L4.

2.4 Diagnosis of Osteoarthritis

There are no specific investigations for diagnosing osteoarthritis. OA diagnosis is purely based on detailed history, complete physical examination and specific radiological investigations. But it is wise to investigate them before initiation of our treatment, because they might have received treatments with NSAIDs (sometimes double or triple analgesics) and including steroids (oral, parenteral or intra-articular) and sometimes, they might have tried modes of treatment options available under the sun and further, as we are going to treat a disease of above middle age, it is always better to rule out comorbid conditions.

2.5 Laboratory Investigations

Counts are usually normal, normocytic hypochromic anaemia, occasionally neutrophilia can be present, due to an acute episode of arthritis and synovial effusions, infection (iatrogenic) or by osteonecrosis. Acute phase reactants like ESR and CRP are normal or can be raised due to above said reasons and in erosive hand OA.

Doing RFT is mandatory in all cases of OA. Always, it is best to do before and after initiation of NSAIDs, and DMOADs. In the presence of elevated or upper limit of normal RFT, beware about initiating or continuing NSAIDs, colchicine and diacerein. Mere presence of hyperuricemia is not at all a label for the diagnosis of gout or for even for initiating treatment for crystal arthritis. Do not reflexively ask patient to take allopurinol, febuxostat just after seeing the value of elevated uric acid. Even a single dose of allopurinol is enough to cause or precipitate renal failure. Rather, the presence of hyperuricemia may be a clue for diagnosing plaque or non plaque psoriasis, as it is probably due to rapid cells turnovers. Serum calcium estimation is not only useful for supplementing or treating for bone mineral loss or replacement but it is occasionally useful to identify, the suspected cases of Paget's disease (with back pain, knee pain and deformity), hyperparathyroidism. Avoid NSAIDs in diabetic with OA as they often has cardio-nephropathy and neuropathic joints. Sometimes, doing AST, ALT, alkaline phosphatase and s. amylase are helpful in some or all cases of OA. I have seen and heard that, number of patients with OA are known chronic alcoholic and often addict to one or other form of spirits. Alcoholics, their readymade comment is "I took it only to relieve pain". By virtue of age and preexisting obesity, they are further prone for weight gain, hyperuricemia, gastroduodenal ulcers, chronic pancreatitis and hepatic complications, and including fatty liver.

Newer serum biochemical markers for cartilage and bone turnover- for Type I and Type II collagen markers like – C & N terminal – telopeptide and COMP can be useful but it is difficult to do in routine clinical practice.

Urine analysis, though appear simple, it gives lot of information for the management of OA. Even before alteration of biochemical parameters, history of oliguria in NSAID received patients is the important clue for its toxicity. Look for albuminuria, if present, order for 24 hours UAE (urinary albumin excretion) and presence of new onset haematuria and RBC cast which can be caused by tubulointerstitial injuries by NSAIDs. Never forget crystals, demonstration of various crystals in urine are helpful for labeling diagnosis and management. Likewise, just by urine tests, we can identify the site of pathologic lesions of the joints by estimating COMP (cartilage oligomeric matrix protein), keratan sulphate, hyaluronan, type III collagen N terminal –propeptide and glucosyl galactosyl pyridinoline but yet no standardized ways of estimating these molecules and it need further study.

Vitamin D3 found to be useful either to prevent or slow the progression of OA. As per Indian study, 70% of populations are having Vitamin D3 deficiency due to lack of facility for Vit. D3 fortified food, poverty for balanced diet and lack of exposure to sun, even in sun plenty country of ours. Serum Vit. D3 less than 20 ng/ml, denotes deficient person, 21-29ng/ml indicates are insufficient and more than 30 ng/ml is sufficient. Sometime, these laboratory tests are done, only to rule out inflammatory arthritis in the given situation of erosive hand OA, and generalized OA or occasionally rheumatoid disease per se can coexist with OA. In fact, RF can be positive in low titer even in simple osteoarthritis as in general population.

Synovial fluid analysis is not mandatory in osteoarthritis. Occasionally it can be done, to determine the cause of arthritis, particularly to rule out inflammatory or crystal arthritis. Joint fluid is usually sterile, clear, yellowish white, viscous and form 4 to 5 cm string (string test) and cell counts are about 200 cells per cmm^3, mostly of lymphocytes. In inflammatory arthritis and crystal induced arthritis, viscosity is increased and cell counts vary from 2000 to 20,000 per cmm^3, and mostly of neutrophils. Synovial glucose is as that of plasma level and protein is usually half the value of serum, and if it is raised, indicates underlying infection as the cause. Uric acid is usually high in gouty arthritis. Synovial fluid LDH estimation may show increased levels in RA, gout and septic arthritis. Unless there was an iatrogenic infection, synovial fluid is negative for bacterial growth. In post traumatic effusion, fluid is either haemorrhagic or serosanguinous, with hemosiderin pigments. Synovial fluid analyses are never complete, without looking for crystals in synovial fluid.

Whenever recalcitrant synovial effusion or persistent arthritis is present, never forget to look for crystals. Confirming the crystals are generally considered as the gold standard in clinically suspected cases of crystal induced arthritis. Synovial fluids contain a number of crystals, such as MSU (monosodium urate), CPPD, HA, BCP, cholesterols and particulate matters like degenerated cartilage, synovial fragments, fibril or rice bodies and occasionally steroid crystals can be seen if they have received intra-articular procedures etc.

Whenever synovial fluid on macroscopic examination per se appear as white solid and chalky deposits, it denotes gout and it can be proved by demonstration of crystals and if aspirate appear as milky paste or liquid, it suggest HA disease and gold glistening appearance can be due to cholesterol laden chronic shoulder effusion or an aspirate from olecranon bursae.

The standard approach for crystal examination, aspirated joint fluids, first to be examined under light microscope and usually crystals are found near the edge of the cover slip, and sometimes, it can be seen inside the cells. Monosodium urate crystal appear as long slender needle and it can be up to 30µ whereas CPPD crystals of 3-7µ size are look like rhomboid and square in shape. HA crystal present as round and shining solid deposits of about 3-15µ.

Oil immersion may help to identify small crystals like cholesterol, cartilage or synovial fragments and its all appears as small, round, and glistening bodies, respectively. There are chances of missing to pick up crystal by light microscopy and it may be due to erroneous aspiration from adjacent sympathetic effusion or due to missed attempt in successful collection of sample. Whenever, doubt arises or still when you strongly suspect the etiology as crystal disease, it is always, better to send the sample for polarizing microscopy.

2.6 Radiological Investigations

Among non invasive investigations, x-rays play an important role in diagnosis and assessing prognosis or progression of osteoarthritis of different joints. Though it is helpful in OA, we may miss to diagnose early OA where cartilage degeneration is the primary pathology. Theoretically speaking, MRI, power doppler and of course, arthroscopies are there for early OA assessment, but the radiological features of mere joint space narrowings are nothing but due to cartilage losses. To pick up, pathological features of OA, the proper positioning, views, and penetrations of the x-rays are vital. Let me discuss about the x-rays of most the common to the least common joints of OA.

2.7 X-rays of knees

Do's

Always ask for x-rays of both knees – AP in standing (weight bearing) either in straight extended view (SEV) or in 15º fixed flexion view (FFV) with buttock touching on x-rays plate and lateral views are taken in perpendicular to AP in standing or else can be taken in sitting with knee in 90º flexion, and skyline view at 30º knee flexion to look for superior patellofemoral joint. Order for AP in standing view (FFV) with under penetration for the suspected cases of CPPD and HA crystal diseases.

Don'ts

Never take knee x-rays in lying (except in bedridden, and when they are unable to stand).

Never attempt to take unilateral knee, because that knee pain may be a complication of opposite knee pathology by unnoticed change in gait, and with one knee X-ray, we can't design to provide footwear modification. Unilateral knee x-rays may be useful only for fracture etiology.

Uses of these views

1) AP standing view is helpful to assess all the features of OA, CPPD and including condylar displacement
2) Skyline view is useful for chondromalacia, patellofemoral JS (Joint Space) and subluxation of patella
3) Lateral view for patellofemoral JS, CPPD, wrapping of patella etc.

2.8 Pitfalls in X- rays of knee

Unilateral X-rays not at all helpful in the management plan of OA. When patients come with severe varus deformity, radiographer may find it difficult to accommodate in AP view. In that case, we must ask radiographer to take x-ray knee AP in standing view of individual leg subsequently.

What are all the features to look for in knee X-rays?

Whenever happen to see the following radiological features, think of primary OA.

Primary OA

a) Eburnation
b) Asymmetrical Joint space narrowing
c) Minimal soft tissue swelling
d) Subchondral sclerosis or enchondral sclerosis
e) Intercondylar spike
f) Osteophytes (usually large)
g) Condylar displacement or subluxation
h) Subchondral cyst
i) Usually no osteoporosis but rather osteosclerosis
j) Patellar dislocation
k) Varus or valgus deformities
l) Condylar enlargement
m) Erosions with sclerotic borders
n) Osteophytic fractures
o) Loose bodies or rice bodies in joint spaces
p) Complete loss of joint spaces in all three compartments
q) Complete loss of architecture of knee joints.

Box 2: Kellgren and Lawrence Grading of Knee Osteoarthritis

Grade of Osteoarthritis	Description
0 – None	No radiographic findings of osteoarthritis
1 – Doubtful	Doubtful narrowing of joint space and possible osteophytic lipping
2- Minimal	Definite osteophytes, definite narrowing of joint space
3- Moderate	Moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone contour
4- Severe	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour

Secondary OA

Whenever happen to see the following radiological features, think of Secondary OA……?

a) Uniform joint space narrowing
b) Marked soft tissue swelling
c) Osteoporosis
d) Osteophytes less commonly present, if present only small marginal
e) Enchondral or subchondral sclerosis is less prominent
f) Subchondral cysts are present
g) Subluxation and deformities are common
h) Pathological fractures can be present
i) Fibrosis or bony ankylosis with complete loss of architecture of joint
j) Condyle sizes are usually normal

2.9 Treatment of Osteoarthritis

In this article, we are not dealing about all the available treatment options for the OA knee. But before they land up here, almost all patients have tried all modalities of treatments like non pharmacological, pharmacological, traditional, native, siddha, ayurveda, quacks, acupunctures, tai chi, mud-pack therapy and including intra-articular procedures, etc. Still, we are having belief in non pharmacologic treatments like patients group discussion on osteoarthritis, value of physical rest after an exertion or manual work, weight loss and the art of living with OA. Along with intra-articular viscosupplements, orthotics like footwear modification, knee taping, splints, walking cane and knee braces are useful methods of management for osteoarthritis of knee.

2.10 Intraarticular Procedures

Viscosupplementation (Intra-articular Hyaluronic Acid Injection)

Hyaluronic acid is a normal constituent of any joints, and it is essential for joints to move without friction. There are various strength and weight of (10,000 to 73,000 Daltons) hyaluronic acid are commercially available and these can be administered intra-articularly into knee, and other joints. After intra-articular HA, they can experience relief from pain and regained mobility and it can last long for several months.

3. Review of Literatures

Systematically, we have reviewed the published case or study reports on osteoarthritis with intra articular injections of viscosupplements. Only few reports are available with head to head to comparisons with hyaluronic acid based on molecular weight. Likewise, none of the case study has revealed that they were given the viscosupplements into joint cavity with the help of image intensifier like C-arm and it seems that they have given by routine sub-patellar route. Thus, we have decided to use HA, either by C- arm guided or by blind sub-patellar approach in delivering viscosupplements and to assess the value and benefits of correctly placing HA into the joint cavity and look for the differences between blind routine sub-patellar route and the duration of the efficacy of HA based on low molecular and high molecular weight and the role of steroid when I add with HA in both low and high molecular viscosupplements

In 2002, Ghosh P et al has studied the benefits HA in osteoarthritis knee, based the molecular weight of viscosupplements. As he stated, high molecular weight HA, when it given into the joints cavity, by virtue of high density, it stays well in the joints without getting absorbed in the synovial fluid circulations and they concluded that HA can form a pericellular coat around cells, interact with proinflammatory mediators, and bind to cell receptors, such as cluster determinant (CD)44 and receptor for hyaluronate-mediated motility (RHAMM), where it modulates cell proliferation, migration, and gene expression and all these physicochemical and biologic properties of HA have been shown to be molecular weight (MW) dependent.[17]

As per case review in the journal of Canadian family physicians by Aggarwal A et al in 2004, they did systematic review on Medline, pre-medline, cochrane databases using MeSH with key words using osteoarthritis of knee and HA for the effectiveness of HA in OA knee and they have found, five case series and 13 RCT and they were critically analysed. In these, three case series and 3 RCTs using high molecualr weight HA, demonstrated to have significant improvement in pain, levels of activities, and functions and they have observed from these studies that viscosupplements, though the benefits of relief from the symptoms are slow but gives long lasting effects whereas steroid give quick relief from their pain.[18] Similar, a meta-analysis of randomized controlled trials was done by Wang C T et al in 2004, has revealed that,safety and therapeutic benefits are present with intra articular injection of HA with minimal side effects.[19]

Vitanzo P C, Sennett B J et al, n 2006 has did study on hyaluronans in OA knee and they wanted to know the effectiveness of HA based molecular weight. They have observed that high molecular weight HA exert not only reduces pain by mechanical effects and it is also by biological functions.[20]

During 2009, RR Bannuru, NS Natov et al, did meta-analysis in OA with HA with corticosteroid, and concluded that corticosteroids appeared give more effective than hyaluronic acid in the short term (up to four weeks) and hyaluronic acid appeared more effective in the long term (four to 26 weeks).[21]

A multi-center, randomized, open-label, non-inferiority trial conducted by Ishijima M, Nakamura T et al for the comparison of intra-articular HA with oral NSAIDs drugs for OA,[22] and another similar was conducted by Bannuru RR, Natov NS et al, they inferred from their study that intra-articualr HA shown to reduces pain, improve mobility and it long lasting as against NSAIDs which often give symptomatic pain relief, but the risk of of NSAIDs outweigh the benefits.[23]

In 2016, Xing D, Wang B et al did systematic review of overlapping meta-analysis based on the PRISMA guidelines on OA knee with intra-articular HA in relation with molecular weight. In this study too, they found to have high molecualr weight HA, demonstrates that is an effective intervention in treating knee OA without increased risk of adverse events.[24]

Recently, in 2018, Altman R, Bedi A et al conducted systematic review on the effects of intra-articular HA in OA knee. The general anti-inflammatory effects of HA in knee OA, mediated through receptor-binding relationships with cluster determinant 44 (CD44), toll-like receptor 2 (TLR-2) and 4 (TLR-4), intercellular adhesion molecule-1 (ICAM-1), and layilin (LAYN) cell surface receptors. Higher molecular weight HA (HMWHA) promotes anti-inflammatory responses, whereas short HA oligosaccharides produce inflammatory reactions. In conclusion, intra-articular HA is a viable therapeutic option in treating knee OA and suppressing inflammatory responses. HMWHA is effective in suppressing the key macromolecules that elicit the inflammatory responses which are triggered by short HA oligosaccharides.[25]

To know the effect of viscosupplement on osteoarthritis of knee, we have carried out, Nested Prospective Open Case Control Comparative Study of Intraarticular Injection of Low and High Molecular Weight Viscosupplement With and Without Steroid in Osteoarthritis of Knee and Look for the Frequency of Requirement for Repeat Dose of Hyaluronic Acid (HA) and to Assess the Use of C-arm in Target Delivery of Viscosupplement into Joint Cavity as Against Routine Practice of Giving HA through sub-patellar route.

Aim

- To study the role of viscosupplement in osteoarthritis of knee joint from KL grade-2, 3 and 4.
- To compare the efficacy between low with high molecular weight viscosupplements.
- To assess the frequency of its use when it was given with and without Steroid.
- To study the role of C-arm in intra-articular viscosupplementation of OA knee,

Objective of the Study

Indians become affluent and most of them are obese and fortunately, their life expectancy has been increased, only to welcome the early onset of osteoarthritis, and in particular OA knee. Unfortunately, just because of the hard work, it never even leave the poor. Sadly, whether they are rich or poor, they vehemently oppose or reluctant to accept for the surgical replacement of joints. Thus, to study the effect of intra-articualr injection of low molecular and high molecualr weight (20,000 and 60,000 daltons) viscosupplement in OA knee with and without steroid and look for the frequency of requirement for repeat dose of HA and to assess the use of C-arm in delivering viscosupplement into joint cavity as against routine practice of giving HA through sub-patellar route.

Inclusion Criteria

Whoever wishes to give written informed consent
Male or female of any race with ages 35-80 years
Osteoarthritis of knee diagnosed with KL grades 2 to 3
Who has joint pain ≥ 40mm on VAS (Visual Analog Scale) at base line
Who is willing for invasive intra-articular injections
Who is wish to stop their pain medications for osteoarthritis except paracetamol

Who are willing for lifestyle modifications, periodic visits, adhere to treatment, basic investigations?

Exclusion Criteria

Cases are not willing or refuses to give consents for intra-articular injections
Who has unstable knees
Who has K.L Grade-4 with subluxation or dislocation or with virtual loss of joint space
Those have had received any intra-articular injection treatment
Known cases of secondary osteoarthritis like rheumatoid, psoriatic arthritis etc
Those with previous history of septic arthritis
Known cases of PLHA (People Living with HIV and AIDS) and HBV and HCV Liver diseases,
Cases with poorly controlled diabetes
Cases who have undergone total knee replacement
Cases with previous history of drug allergy
Cases who are all on regular intake of anticoagulants drugs
Cases with local areas of skin infections at or near knee joints.

4. Material and Methods

We have enrolled 358 patients (104 males and 254 females) of osteoarthritis of knee with radiological Kellgren and Lawrence (K&L) grades 2 to 4 based on X-rays of knee taken in AP in standing view.(Fig.3) Pain was evaluated by VAS, and performance was assessed by 50 foot walk time.

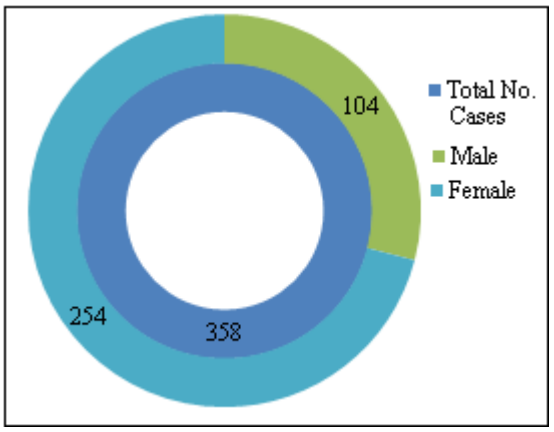


Figure 3: Demographic Data

We categorized the patients into KL grade 2 (M 24 & F 82); KL grade 3 (M 41 & F 112) and KL grade 4 (M 39 & F 60). (Fig.4)

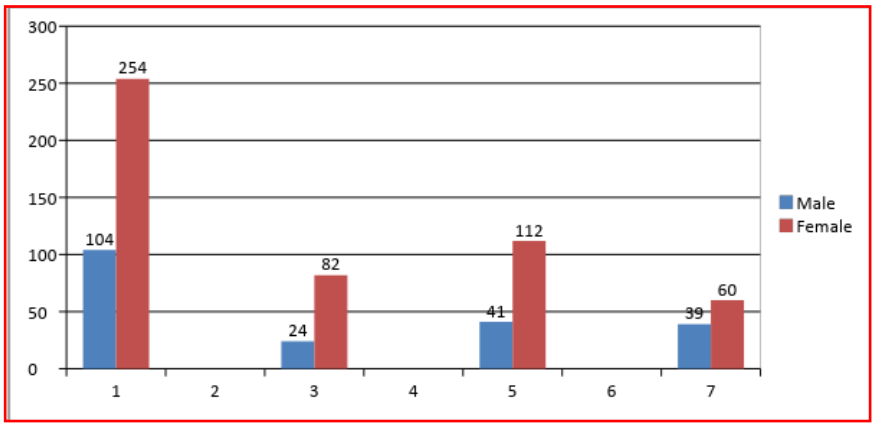


Figure 4: Category of cases based on KL Grades

We have randomly picked up and formed into group-A & B. 178 cases are kept in group-A with KL grade-2 (M22 & F37), KL grade-3 (M27 & F52) and KL grade-4 (M21 & F19). In group- B, we have selected 180 cases from KL grade-2 (M24 & F44), KL grade-3 (M29 & F40) and KL grade-4 (M 19 & F 24). (Fig.5)

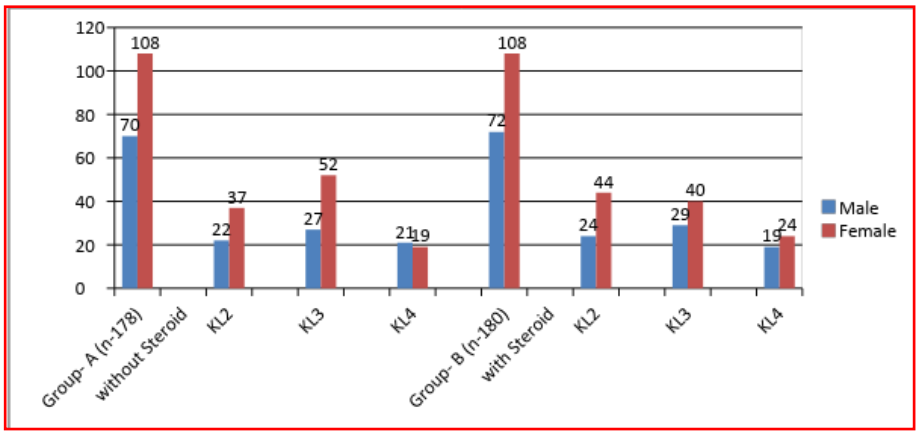


Figure 5: All cases divided and formed as Group-A (without steroid) & Group-B (with steroid)

In group- A (n-178), 85 cases allotted for low (M32 & F53) and 93 cases for high (M40 & F53) molecular weight viscosupplement without steroid and it was kept as control for Group-B. In group-B (n-180), 86 cases have been selected for low (M32 & F54& and 94 cases for high (M40 & F54) molecular weight viscosupplement with steroid. (Fig.6)

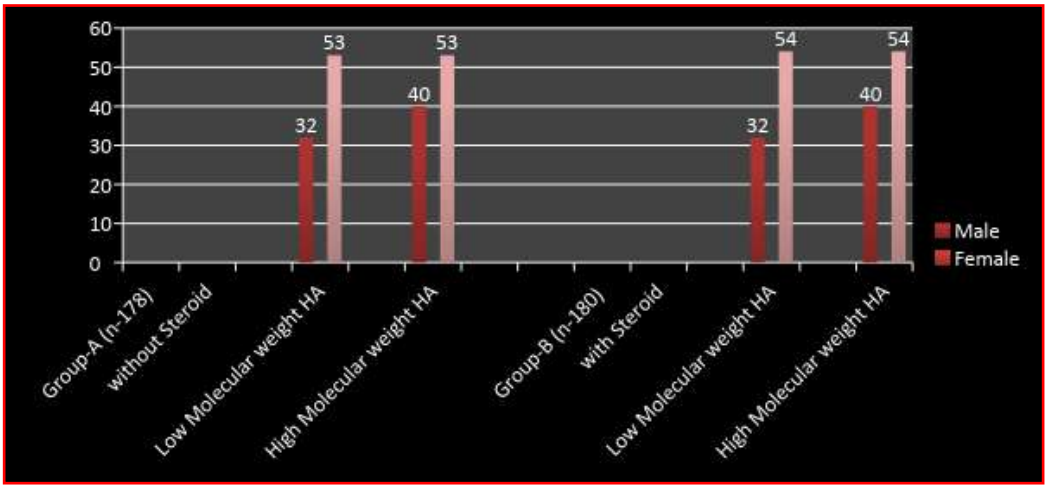


Figure 6: Group-A and Group-B cases categorized for Low and High MW viscosupplement

The low molecular weight HA was given as weekly once for five weeks and high molecular weight viscosupplement was given as single dose. From group- A and B, we randomly selected 211 (60.75%) cases (37 & 52 from group- A and 40 & 82 from group- B) for assessing the role of C- arm in delivering viscosupplements into knee joint cavity, because knee joint cavity is well away from sub-patella and in KL grade 3 and 4, joint cavity is narrow or asymmetrically present with valgus and varus deformity and thus, viscosupplement was given under the guidance of C-arm for appropriate target delivery. (Fig.7)

Figure 7: Targeted Injection of Viscosupplement in to the knee joint cavity

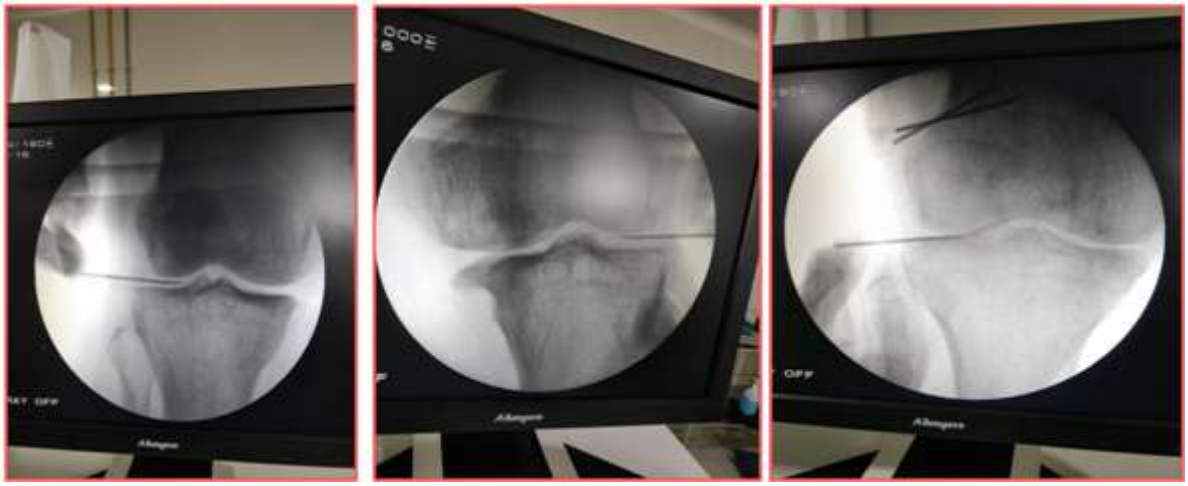
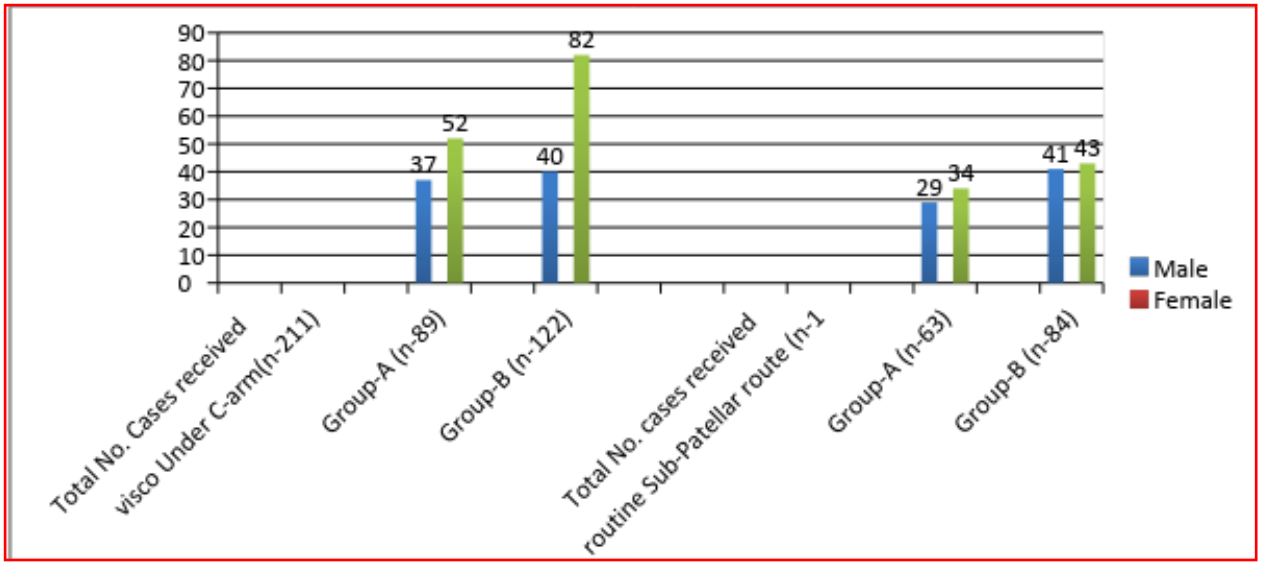


Figure 8: C-Arm guided and sub-patellar route viscosupplementation



We asked them stay in bed for 8 to 24 hours for the even distribution and allow the HA to get complete percolation in the fissured cartilages and for the remaining cases, viscosupplement was given into knee joint as the routine sub-patellar route on lateral approach.

5. Results

Mean age of patients 52.4 years (range 39-74 years); with male: female ratio of 1:2.44. Early feel good response in group-A and group-B were assessed by VAS from 0 to 100. Before and after the viscosupplementation, visual analogue scale was compared with both group. In group-A, before viscosupplement, 100% pain was noted in 82 patients, and 50% pain was seen in 61 cases, whereas after viscosupplementation, more than 50% pain relief was noted in 92 cases (31 in LMW HA and 61 cases in HMW HA). (Fig.9,10).

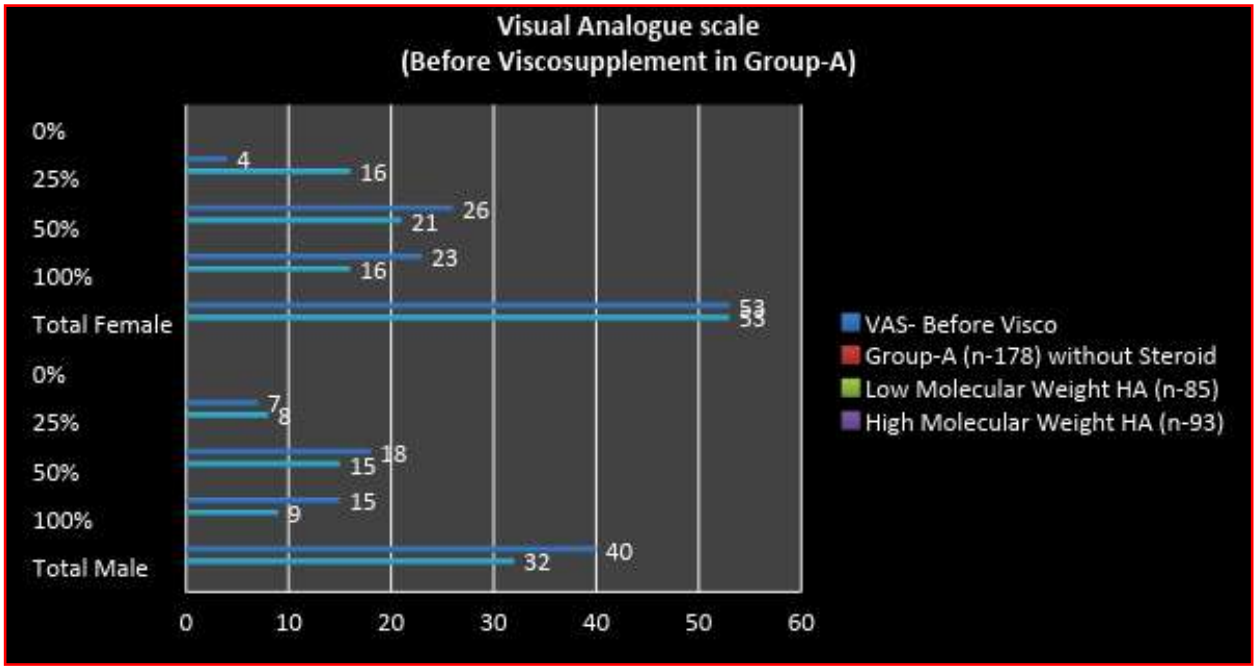


Figure 9: Visual Analogue Scale –Before Viscosupplement in Group-A

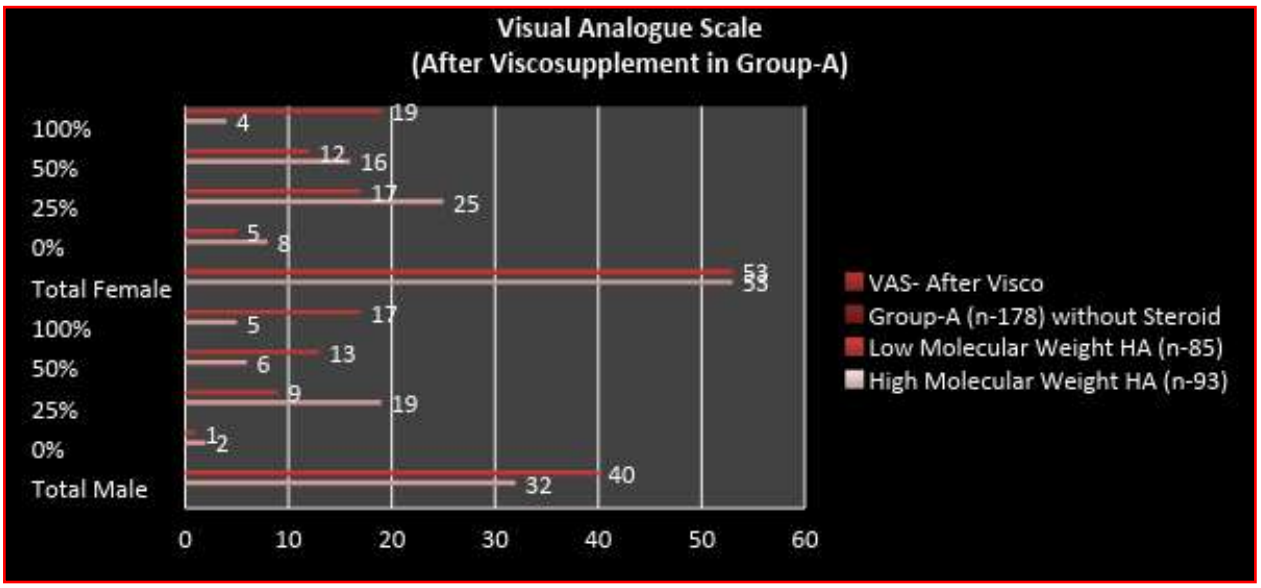


Figure 10: Visual Analogue Scale- After Viscosupplement in Group-A

In group-B, as per VAS, 100% pain in 85 patients and 50% pain in 70 patients are have been noted, whereas after HA, more than 50% pain relief and early feel good response was noted in 152 patients (68 in LMW HA and 84 patients in HMW HA). (Fig.11,12).

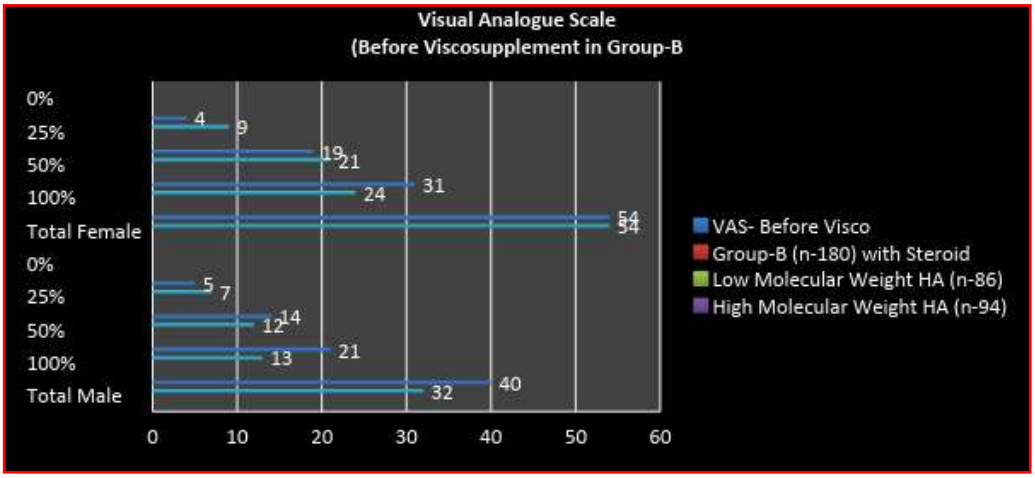


Figure 11: Visual Analogue Scale –Before Viscosupplement in Group-B

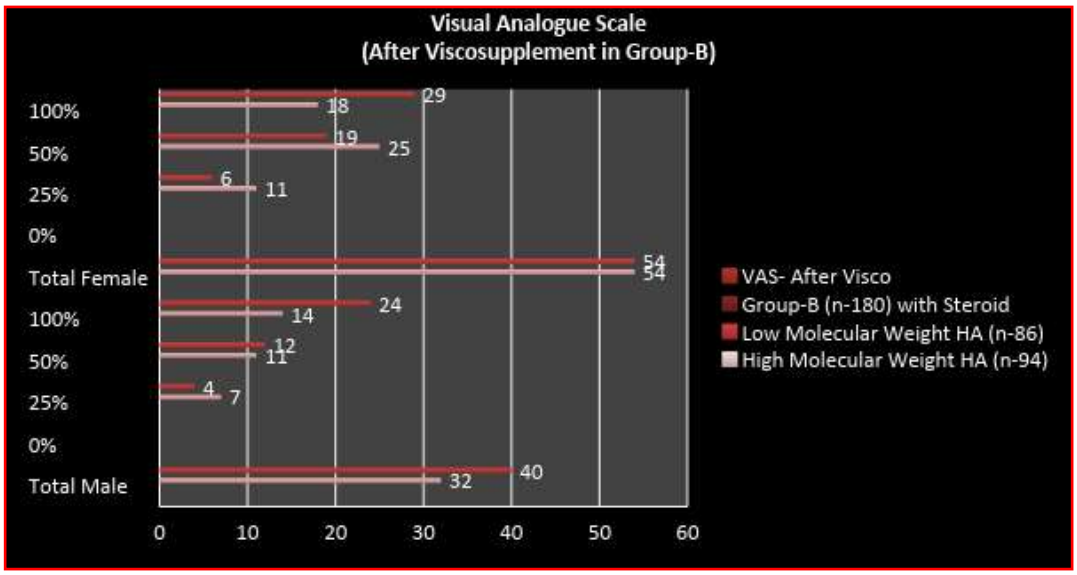


Figure 12: Visual Analogue Scale- After Viscosupplement in Group-B

Pre and Post procedures, the performance was assessed by 50 foot walk time. In group-A, in low molecular weight HA category, before viscosupplement, they take 76 seconds to finish 50 foot walk and whereas after the procedure, they able to complete 50 foot walk in 68 seconds, and in HMW HA category, before visco, they need 68 seconds, and after the visco, only 42 seconds are required to complete the target. In group-B, in low molecular weight category, before the procedure, patients took 72 seconds for 50 foot walk and whereas after the procedure, only they needed 36 seconds and in HMW HA category, before visco, it was 81 seconds and after visco, they quickly complete 50 foot walking distance in 26 seconds. (Fig.13,14)In this study, we have looked in to the role and benefits of C-arm for the administration of viscosupplement, and it reveals that, C-arm guided hyaluronic acid directly in to the joint cavity cases are performing well and they have long lasting effect, as 31% in LMW HA and 64% in HMW HA in group-A, and in group-B, 73% and 98% in low and high molecular weight viscosupplement, respectively. In those who have received viscosupplement through conventional sub-patellar route, their results are not satisfactory than C-arm guided, and it was found in group-A with low MWHA at 14%, and in high MWHA at 36% and whereas in group-B, 48% in low MWHA with and 59% are in high molecular weight HA.

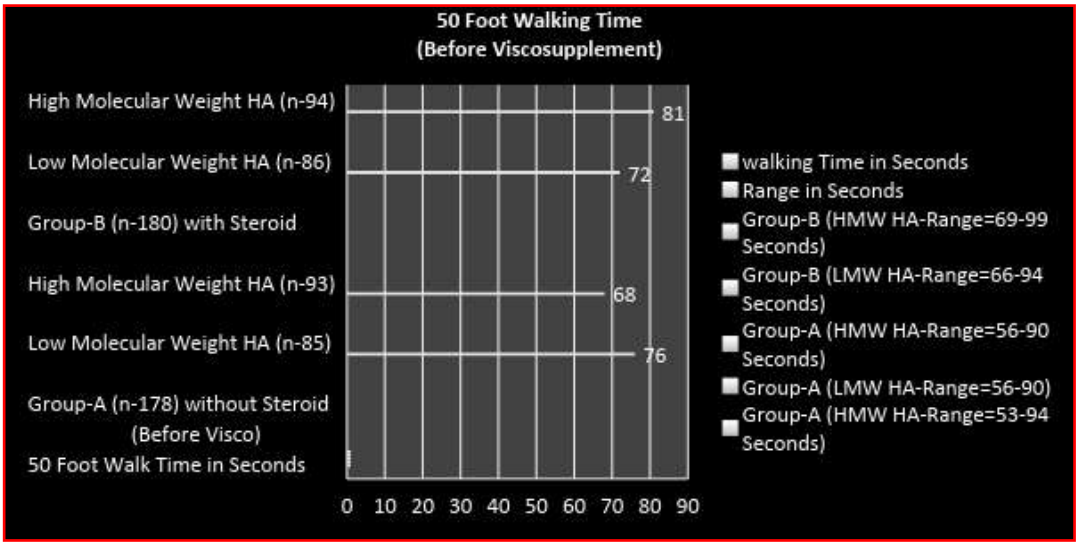


Figure 13: 50 Foot Walking Time- Before Viscosupplement in Both Group- A & B.

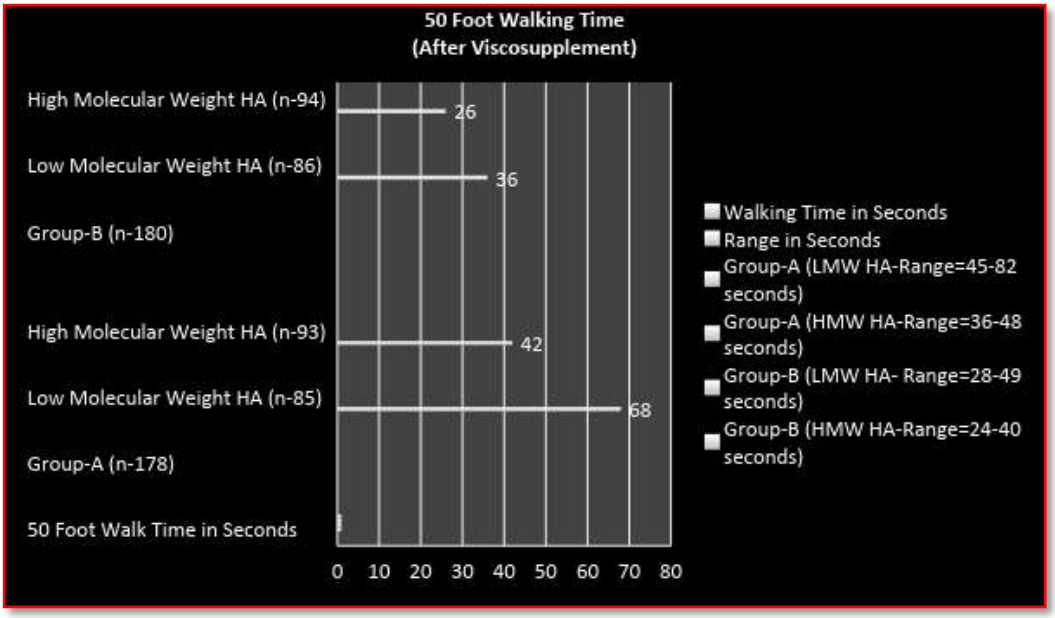


Figure 14: 50 Foot Walking Time- After Viscosupplementation in Both Group-A & B.

After 3rd, 6th, and 9th month follow up, 34% in group-A and 86% in group-B with high MWHA patients had high level performance in pain free walk and gait and whereas at 24th month follow up, still 59% of the group-B patients with high molecular weight HA with steroid, continue to have high level performance without NSAIDs whereas in group-A with low MWHA without steroid had no benefits was noted at 3rd month review and in group-B with low molecular weight HA with steroid has persistence of pain free walk, 38% at 3rd month, and 17% at 6th month and beyond that, no appreciable responses was seen by them. (Fig.15)

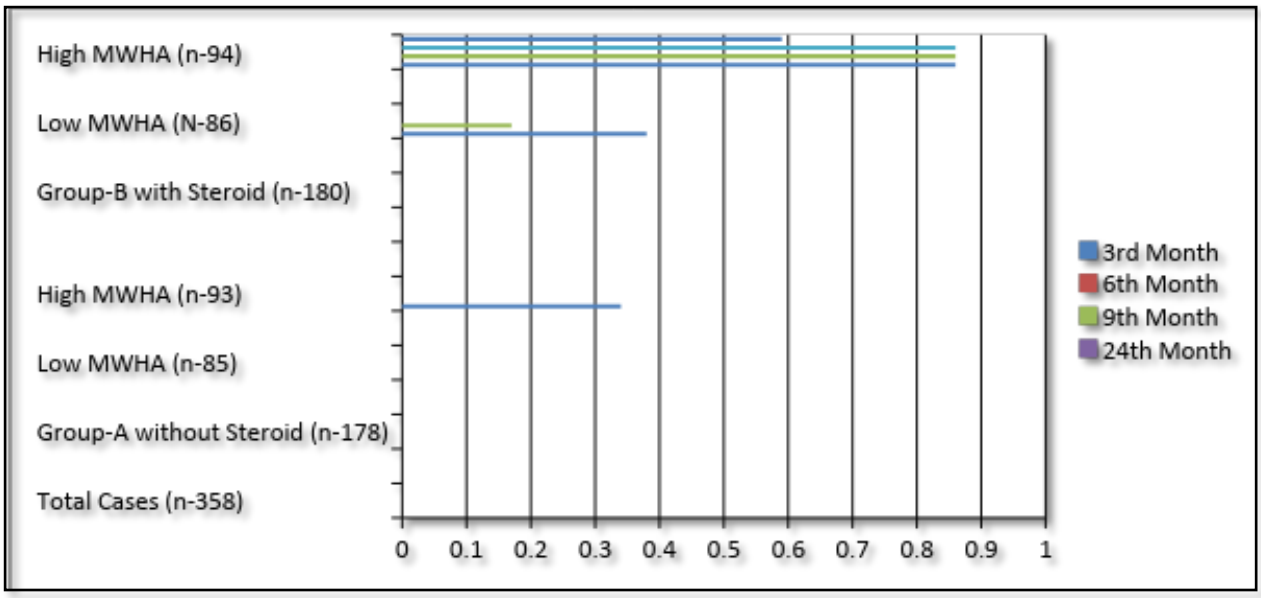


Figure 15: Study cases follow up in 3rd, 6th, 9th and 24th month of viscosupplementation

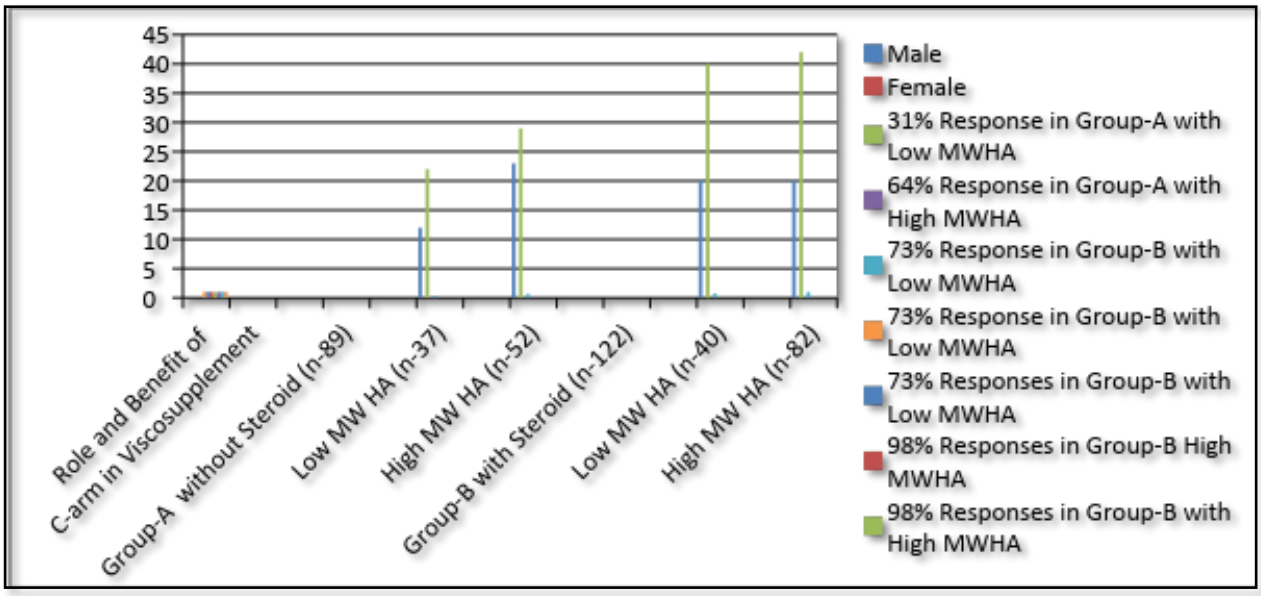


Figure 16: Role and Benefit of C-Arm in viscosupplementation in Both Group-A & B

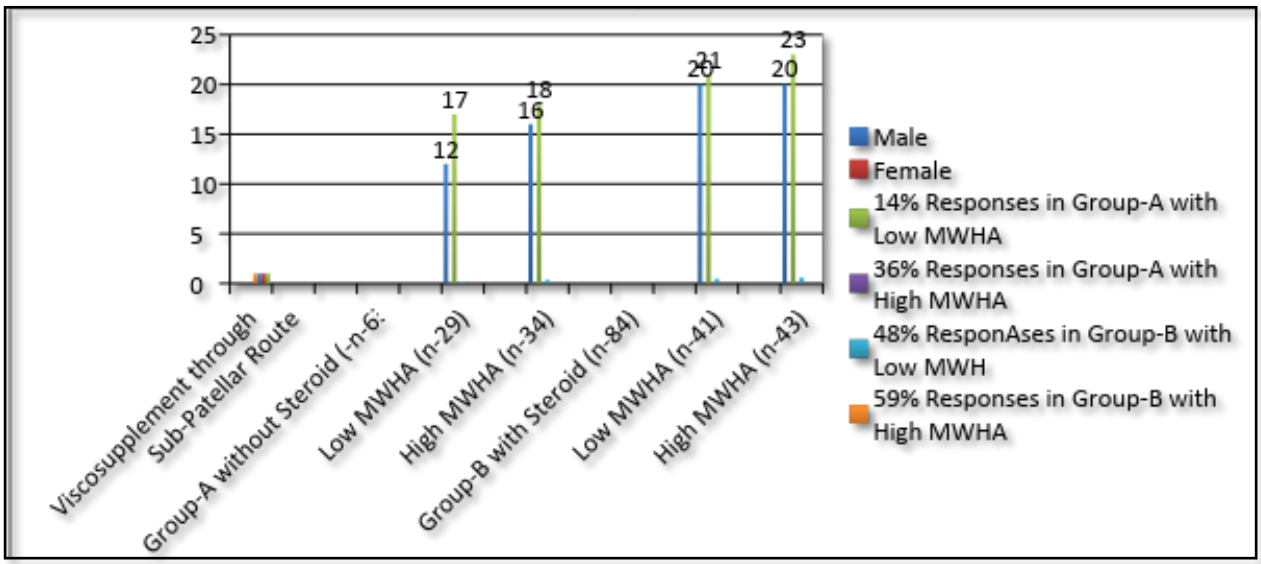


Figure 17: Effect of routine sub-patellar route viscosupplementation in Both Group-A & B

From our study, it clearly reveals that high molecular weight HA in both group A (without steroid) and group-B (with steroid) are having excellent clinical benefits in osteoarthritis of knee and its statistical analysis with student-t test in both group-A and B category are having the p- value of 0.0001 whereas low MWHA in both group-A and B are not statistically significant. Likewise, early feel good responses, reduction in pain and swelling are good in high molecular weight category (61 cases in group-A & 84 cases in group-B). 50 foot walking time, in group-A, improvement was noted from 76 to 68 seconds with LMW HA and from 68 to 42 seconds with HMW HA, and whereas, in group-B, remarkable benefits was seen, that is 72 seconds to 36 seconds in LMW HA and 81 seconds to 26 seconds in HMW HA and statistically extrapolating the 50 foot walk time in both group-A & B, has shown the P-value of 0.001 and it infer that, this value is statistically significant for high molecular weight viscosupplements. Next repeat dose for high molecular weight HA in both group- A & B and with those with KL grades-2 & 3 are not required even at 24th month of visit but 28% of KL grade-4 cases, required repeat dose after about 6 to 12 months. The missing for next doses are high in both group-A and B category of low MWHA with 34% (28.9 cases) and 21% (18.06 cases), respectively.

6. Discussion

Around the world, osteoarthritis is the second leading cause of morbidity as against as the coronary heart disease and it still hold unshakable in the first place. Most of the Indians are become affluent and fortunately their life expectancy has been increased. But unfortunately, quite large numbers of them are obese at young and middle ages for only to welcome the early onset of osteoarthritis, and in particular OA knee. Regretfully it never even leave the poor and the bread winner of the family, OA will affect them, just because of their hard work in field, mines, manual workers and sometime, it is the biggest problem in athletes and marathon runners. Most of the time, earlier symptoms often are mild and often, they themselves ignore it, or not recognized by the treating primary care physician and ultimately results in complete anatomical damages like narrowing of joint space, osteophyte formation, condylar displacement, enchondral sclerosis, subluxation or dislocations of knee joints and with secondary osteoporosis etc.

To admit the truth, whether they are wealthy or penniless, they all vehemently oppose or reluctant to accept for the surgical replacement of joints. Thus, this study was carried out to know the effect of intra-articualr injection of low and high molecular weight (20,000 to 60,000 daltons) viscosupplement in OA knee and it was done with and without steroid and look for the frequency of requirement of repeat dose of HA and to assess the role and benefit of C-arm in target delivery of HA into knee joint cavity as against routine practice of blindly giving viscosupplement through sub-patellar route.

HA is a viscous solution with a molecular weight (200,000-730,000 daltons) fraction of purified natural sodium hyaluronate in buffered physiological sodium chloride, having a pH of 6.8-7.5. The sodium hyaluronate is extracted from rooster combs. Hyaluronate is a natural complex sugar of the glycosaminoglycan family and is a long-chain polymer containing repeating disaccharide units of Na-glucuronate-N-acetylglucosamine.

As discussed in review, In 2002, Ghosh P et al has studied the benefits HA in osteoarthritis knee, based the molecular weight of viscosupplements and reviewed in vitro and in vivo reports to identify the pharmacologic activities of HA in OA knee. The high molecular weight HA, when it given into the joints cavity, by virtue of high density, it stays well in the joints without getting absorbed in the synovial fluid circulations and they concluded that HA can form a pericellular coat around cells, interact with proinflammatory mediators, and bind to cell receptors, such as cluster determinant (CD)44 and receptor for hyaluronate-mediated motility (RHAMM), where it modulates cell proliferation, migration, and gene expression and all these physicochemical and biologic properties of HA have been shown to be molecular weight (MW) dependent. Like this, in our study, high molecular weight given OA patients has shown long lasting improvement in their pain and mobility even 6 months after the viscosupplement, they had on functional well being is maintained.[17] Similarly, in our study, these effects was noted in group-A & B patients, who have received high MWHA and the effect was last long even for 24 months.

As per case review in the journal of Canadian family physicians by Aggarwal A et al in 2004,[18] they did five case series and 13 RCTs were critically appraised and systematic review on Medline, pre-medline, cochrane databases using MeSH with key words using osteoarthritis of knee and HA for the effectiveness of HA in OA knee. Similar, a meta-analysis of randomized controlled trials was done by Wang C T et al in 2004,[19] has revealed that,safety and therapeutic benefits are present with intra articular injection of HA with minimal side effects. Our study is randomized, prospective study on active OA knee, directly observed the practical improvement in signs and symptoms of all spectrum of cases and we found that high molecular weight group patient did well at 6 months and at 2 years follow up, but quick relief from pain and early feel good responses were excellent in those who received steroid along with HA and as per their study, low molecular weight HA continue shed conflicting results.

Vitanzo P C, Sennett B J et al, n 2006 has did study on hyaluronans in OA knee and they wanted to know the effectiveness of HA based molecular weight. They have observed that high molecular weight HA exert not only reduces pain by mechanical effects and it is also by biological functions.[20] During 2009, RR Bannuru, NS Natov et al, did meta-analysis in OA with HA with corticosteroid, and concluded that corticosteroids appeared give more effective than hyaluronic acid in the short term (up to four weeks) and hyaluronic acid appeared more effective in the long term (four to 26 weeks). Exactly, as per these above study results, our pateints has shown prompt 80% improvements with HA with steroid 80% than only 43% with HA alone.[21]

As per trials with head to head to comparison with HA with NSAIDs, multicenter, randomized, open-label, non-inferiority trial conducted by Ishijima M, Nakamura T et al,[22] and another similar study was conducted by Bannuru RR, Natov NS et al, they inferred from their study that intra-articualr HA shown to reduces pain, improve mobility and it long lasting as against NSAIDs which often give symptomatic pain relief, but the risk of of NSAIDs outweigh the benefits.[23] Our study is not correlated NSAIDs, but pain killers necessity was not required in about 68% of both high molecular HA with and without steroid cases.

In Feb. 2018, yet to get printed and published study was carried out by Altman R, Bedi A et al and they have conducted systematic review on the effects of intra-articular HA in OA knee and they come out general consensus that anti-inflammatory effects of HA in knee OA, mediated through receptor-binding relationships with cluster determinant 44 (CD44), toll-like receptor 2 (TLR-2) and 4 (TLR-4), intercellular adhesion molecule-1 (ICAM-1), and layilin (LAYN) cell surface receptors. Higher molecular weight HA (HMWHA) promotes anti-inflammatory responses, whereas short HA oligosaccharides produce inflammatory reactions.[24] In conclusion, intra-articular HA is a viable therapeutic option in treating knee OA and suppressing inflammatory responses. HMWHA is effective in suppressing the key macromolecules that elicit the inflammatory responses which are triggered by short HA oligosaccharides. Our study results are in realities are mostly matching with all the published and even to yet to get published reports that high molecular weight HA lead superior role in pain and functional outcome of osteoarthritis of knee.

7. Conclusion

1) Viscosupplement was found to be useful modality of treatment in osteoarthritis of knee in KL grade 2 & 3.
2) Early feel good responses and reduction pain on visual analogue scale was seen in high molecular weight category of group-A & B cases than in low MWHA categories.
3) On 50 foot walking time;
   a) Group-A cases who have received high molecular weight viscosupplement, they can able to complete in 42 seconds as against 68 seconds before the procedures, whereas
   b) Group-B cases with high molecular category can finish off the 50 foot walk distances in 26 seconds as against 81 seconds before the procedures.
4) Steroid with viscosupplement have quickly relieved their pain and improved the mobility.
5) C-arm is surely useful in target delivery of viscosupplement into the joint cavity, and they perform well in early feel good responses and this effect is last long than when it is administered by blind sub-patellar route.
6) In KL grade-4 OA knee, when they are unfit or not willing for surgery or presence of comorbid conditions, viscosupplement can give 40% functional improvement in pain and gait and 28% might require repeat dose of viscosupplement in 6 months to 12 months.
7) There were no significant differences in response to viscosupplement in both sexes.
8) Weekly doses category patients are missing for the next doses are seen at 34% in group- A and 21% in group-B low molecular weight.
9) Ask them to give “pain killer holiday” whenever, no pain, less or tolerable pain, it is better to bear the pain and put full stop to pain pills.
10) Future of osteoarthritis patients are looks bright, when they report early to appropriate clinician, they can give “not pain free but disease free life”.

8. Closing Statement

Financial or Conflicts of Interest: None

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Appendices

Abbreviations
OA (Osteoarthritis)
Viscosupplement
HA (Hyaluronic Acid)
LMW HA (Low Molecular Weight Hyaluronic Acid)
HMW HA (High Molecular Weight Hyaluronic Acid)
KL grade (Kellgren and Lawrence grade)
AP (Anteroposterior)
VAS (Visual Analogue Scale)
HRT (Hormone Replacement Therapy)